REMARKS

This responds to the Office Action mailed on May 3, 2007.

Claim 64 is canceled, claims 45, 56, 57, and 63 are amended, and no claims are added; as a result, claims 45-63 are now pending in this application. Claims 56 and 57 are amended to correct grammatical errors.

Claims 45 and 63 are amended to recite that the lotion causes more vasoconstriction when applied to living human skin than does a cream containing mineral oil or soft white paraffin, or both, the cream containing the same amount of the fluticasone or the pharmaceutically acceptable salt or ester thereof. Support for this amendment is found, for example,in Table 1 and in Table 2, where the AUC of Cutivate®, a 0.05% fluticasone cream containing a hydrocarbon occlusive agent as described above, and the 0.05% fluticasone lotion are compared. The claimed lotion, lacking the hydrocarbon occlusive agent of Cutivate®, but containing the same amount of fluticasone propionate, is shown to have greater vasoconstrictive activity when applied to living human skin than does Cutivate®. Furthermore, the claimed lotion is shown to inherently possess this property, as was disclosed in the application as originally filed (see Tables 1 and 2). Therefore, the lotion as claimed in claims 45 and 63 as amended herein constitutes the same invention as already has been searched and examined in this application; these amendments do not constitute a different invention that was not earlier constructively elected by prosecution on the merits of claims to another invention.

Cutivate® cream (0.05%) is indicated on the SmithKleinGlaxo website (http://emc.medicines.org.uk/emc/assets/c/html/displaydoc.asp?DocumentID=726 , copy enclosed, Doc. A) to contain 0.05% fluticasone propionate plus: Liquid Paraffin, Cetostearyl Alcohol, Isopropyl Myristate, Cetomacrogol 1000, Propylene Glycol, Imidurea, Sodium Phosphate, Citric Acid Monohydrate, and Purified Water. Liquid paraffin is mineral oil, as is well known in the art. In the Physicians Desk Reference, 2003, p. 1496, (copy enclosed, Doc. B) this liquid paraffin is referred to directly as mineral oil. Cutivate® cream is also characterized as containing 0.05% fluticasone propionate on the FDA website (see http://www.accessdata.fda.gov/scripts/cder/ob/docs/temptn.cfm , copy enclosed, Doc. C). Thus, Cutivate® cream is directly comparable to the inventive fluticasone lotion in terms of fluticasone propionate wt% content, but the lotion lacks the liquid paraffin ingredient of Cutivate® cream.

And, as Table 2 shows, the presently claimed lotion is a more effective vasoconstrictor than is the cream containing the same steroid at the same concentration.

§103 Rejection of the Claims

Claims 45-64 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Gordon (Clinical therapeutics, 1998; 20(1): 26-39) and Hill (WO 92/14472) in view of Richards (US Patent 4,985,4318) and Budavari (Merck Index 11th ed. 1989, monograph 6021 and 7879) references of record in the parent application.

Applicants respectfully traverse the claim rejections and, to the extent they are maintained with respect to the claims as amended herein, request reconsideration and withdrawal of the rejections.

Claim 64 is canceled herein. All other pending claims depend on claim 45, with the exception of claim 63. Claims 45 and 63 both recite that the composition is "free of mineral oil and white soft paraffin." With the cancellation of claim 64, all pending claims now recite a composition that is free of mineral oil and white soft paraffin.

Hill states (p. 2) that "[c]ompositions of the invention can conveniently be formulated in a conventional manner . . . in the form of creams or ointments. . . . Ointments may normally be prepared by melting soft white paraffin (white petrolatum) . . .and blending in a slurry of the drug in a minimum quantity of liquid paraffin." Liquid paraffin is synonymous with mineral oil, as is well known in the art. Hill thus teaches only a composition that is based on soft white paraffin and contains mineral oil. Example 1, the sole example therein, teaches adding 10% soft white paraffin to the composition. Therefore Hill does not teach or suggest a formulation that explicitly includes the negative limitation of an absence of mineral oil and white soft paraffin. Hill teaches only a fluticasone formulation with a hydrocarbon (mineral oil or petrolatum) occlusive agent.

Gordon discusses a formulation for clobetasol, which Gordon characterizes as a "super-high potency ... corticosteroid" (p. 27). It is well known in the art and is disclosed in the present application (p. 1) that mineral oil is occlusive, and that "[o]cclusion in topical drug delivery is known to increase . . . the effectiveness of the steroid." Since adding an occlusive agent is known to increase the effectiveness of a particular amount or concentration of a steroid in

vasoconstriction, it therefore follows that removing an occlusive agent from a formulation containing a particular amount of a steroid would be expected by a person of ordinary skill to reduce the vasoconstrictive potency of the formulation.

The formulation of Gordon is presented only as a formulation containing the super-high potency corticosteroid clobetasol. Clobetasol is also characterized in Table 2 of the present application as being of "high potency" (Temovate® being a proprietary name for clobetasol 0.05% cream, as evidenced by the FDA "Orange Book" website http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm wherein clobetasol propionate 0.05% topical cream is identified as Temovate®, copy enclosed, Doc. D). As a super-high potency corticosteroid, enhancement of bioactivity is not needed or indicated, for example due to well-known side effects caused by overdoses of corticosteroids, such as suppression of the HPA axis (see, for example, information on Temovate® from the FDA website at http://www.fda.gov/ohrms/dockets/dockets/06p0387/06P-0387-EC1-Attach-2.pdf , copy enclosed, Doc. E).

Fluticasone, on the other hand, is characterized as a less potent corticosteroid (see Table 2 of the Specification as originally filed). As such, it was, prior to the present application, being provided as a cream of the proprietary name Cutivate® (see above).

A person of ordinary skill in the art would not seek to diminish the potency of an already less-potent corticosteroid by removing the occlusive hydrocarbon components. Therefore, combining the Hill and Gordon references would not make a fluticasone lotion lacking an occlusive hydrocarbon component obvious to a person of ordinary skill.

Furthermore, claims 45 and 63 are amended herein to recite that the claimed lotion containing a wt% of fluticasone or a pharmaceutically acceptable salt or ester thereof, causes more vasoconstriction when applied to living human skin than does a cream containing mineral oil or soft white paraffin, or both, and the same amount of the fluticasone or the pharmaceutically acceptable salt or ester thereof. Support for this amendment is found, for example, in Tables 1 and 2, as discussed above.

As mentioned above, Cutivate® cream (0.05%) is indicated on the SmithKleinGlaxo website (http://emc.medicines.org.uk/emc/assets/c/html/displaydoc.asp?DocumentID=726, Doc. A), and in the *Physicians' Desk Reference* (Doc. B) to contain 0.05% fluticasone propionate plus:

Liquid Paraffin, Cetostearyl Alcohol, Isopropyl Myristate, Cetomacrogol 1000, Propylene Glycol, Imidurea, Sodium Phosphate, Citric Acid Monohydrate, and Purified Water. Liquid paraffin is mineral oil, as is well known in the art. Thus, Cutivate® is directly comparable to the claimed fluticasone lotion, which also contains 0.05% fluticasone propionate, with the exception that the claimed lotion lacks the liquid paraffin ingredient. And, as Table 2 shows, the lotion is a more effective vasoconstrictor than is the cream containing the same steroid at the same concentration.

The Examiner's allegations that the results of the studies conducted by applicants lack statistical significance simply because of the lack of standard deviation figures (data spread) are unsupportable. The tables are the result of studies of multiple individuals, as is indicated, and the results presented are statistically significant. Of course, statistical significance is never 100%; all that can be indicated is some confidence value that the difference between two sets of data is significant. The data presented are shown as being statistically significant and, absent some indication of error or fraud to the contrary, such data should be accepted as supporting the assertions. Data are presented that 0.05% fluticasone propionate lotion, lacking mineral oil and white soft petrolatum, is more effective for vasoconstriction than is a 0.05% fluticasone propionate cream containing liquid petroleum (mineral oil), i.e., Cutivate®.

None of the cited documents disclose or suggest this unexpected increase in activity in a lotion lacking hydrocarbon occlusive agent. To the contrary, knowledge available to one of ordinary skill in the art would indicate the opposite result. This is clear and convincing evidence of an unexpected result, and according to the holding of *Graham* is a strong secondary indicium of non-obviousness.

Accordingly, a person of ordinary skill in the art would not find it obvious, as stated by the Examiner, to substitute the fluticasone of the preparation of Hill for the clobetasol of the Gordon formulation.

Applicants therefore respectfully request withdrawal of the claim rejections under §103(a).

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney at (612) 373-6903 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

GORDON J. DOW ET AL.

By their Representatives,

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Date 7-24-07 By _____
Warren D. Woessner
Reg. No. 30,440

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: MS AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 24th day of July, 2007.

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Cutivate Cream 0.05%

Table of Contents

AUTHORISATION
10. DATE OF REVISION OF THE TEXT
11. Legal Status

1. NAME OF THE MEDICINAL PRODUCT

Cutivate Cream 0.05%.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Fluticasone Propionate (micronised) HSE 0.05% w/w.

3. PHARMACEUTICAL FORM

Cream

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults:

For the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses such as: eczema including atopic and discoid eczemas; prurigo nodularis; psoriasis (excluding widespread plaque psoriasis); neurodermatoses including lichen simplex; lichen planus; seborrhoeic dermatitis; contact sensitivity reactions; discoid lupus erythematosus; an adjunct to systemic steroid therapy in generalised erythroderma; insect bite reactions; or prickly heat.

Children:

For children and infants aged three months and over who are unresponsive to lower potency corticosteroids Cutivate Cream is indicated for the relief of the inflammatory and pruritic manifestations of atopic dermatitis under the supervision of a specialist. Expert opinion should be sought prior to the use of Cutivate Cream in other corticosteroid responsive dermatoses in children.

4.2 Posology and method of administration

Eczema/Dermatitis

For adults, children and infants aged three months and over, apply a thin film of Cutivate Cream to the affected skin areas once daily.

Other indications

Apply a thin film of Cutivate Cream to the affected skin areas twice daily

Duration of use :

Daily treatment should be continued until adequate control of the condition is achieved. Frequency of application should thereafter be reduced to the lowest effective dose.

When Cutivate is used in the treatment of children, if there is no improvement within 7 – 14 days, treatment should be withdrawn and the child re-evaluated. Once the condition has been controlled (usually within 7-14 days), frequency of application should be reduced to the lowest effective dose for the shortest possible time. Continuous daily treatment for longer than 4 weeks is not recommended

For topical administration.

4.3 Contraindications

Rosacea, acne vulgaris, perioral dermatitis, primary cutaneous viral infections (e.g. herpes simplex, chickenpox). Hypersensitivity to any of the ingredients. Perianal and genital pruritus. The use of fluticasone propionate skin preparations is not indicated in the treatment of primarily infected skin lesions caused by infection with fungi or bacteria. Dermatoses in infants under three months of age, including dermatitis and napkin eruptions.

4.4 Special warnings and precautions for use

Fluticasone propionate has a very low propensity for systemic absorption, nevertheless, prolonged application of high doses to large areas of body surface, especially in infants and small children, might lead to adrenal suppression. Children and infants have a greater surface area to body weight ratio compared with adults. Therefore, in comparison with adults, children and infants may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity. Care should be taken when using Cutivate Cream to ensure the amount applied is the minimum that provides therapeutic benefit.

Long-term continuous use should be avoided in children and infants. The safety and efficacy of fluticasone propionate when used continuously for longer than 4 weeks has not been established.

The face, more than other areas of the body may exhibit atrophic changes after prolonged treatment with potent topical corticosteroids. This must be borne in mind when treating such conditions as psoriasis, discoid lupus erythematosus and severe eczema.

If applied to the eyelids, care is needed to ensure that the preparation does not enter the eye so as to avoid the risk of local irritation or glaucoma.

Topical steroids may be hazardous in psoriasis for a number of reasons, including rebound relapses, development of tolerance, risk of generalised pustular psoriasis and development of local or systemic toxicity due to impaired barrier function of the skin. If used in psoriasis careful patient supervision is important and referral to a dermatologist is required before using Cutivate Cream to treat psoriasis in children and infants.

Appropriate antimicrobial therapy should be used whenever treating inflammatory lesions, which have become infected. Any infection requires withdrawal of topical corticosteroid therapy and systemic administration of antimicrobial agents. Bacterial infection is encouraged by the warm, moist conditions induced by occlusive dressing, and so the skin should be cleansed before a fresh dressing is applied.

Cutivate Cream contains the excipient, imidurea, which releases traces of formaldehyde as a breakdown product. Formaldehyde may cause allergic sensitization or irritation upon contact with the skin.

4.5 Interaction with other medicinal products and other forms of interaction

None known.

4.6 Pregnancy and lactation

Pregnancy: Topical administration of corticosteroids to pregnant animals can cause abnormalities of foetal development, but in humans there is no convincing evidence that systemic corticosteroids cause an increased incidence of congenital abnormalities. However, administration of fluticasone propionate during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

Lactation: The excretion of fluticasone propionate into human breast milk has not been investigated. When measurable, plasma levels were obtained in lactating laboratory rats following subcutaneous administration, there was evidence of fluticasone propionate in the breast milk. However plasma levels in patients following dermal application of fluticasone propionate at recommended doses are likely to be low.

When fluticasone propionate is used in breast feeding mothers, the therapeutic benefits must be weighed against the potential hazards to mother and baby.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 and <1/10), uncommon (≥ 1/1000 and <1/100), rare (≥ 1/10,000 and <1/1000) and very rare (<1/10,000) including isolated reports. Very common, common and uncommon events were generally determined from clinical trial data. The background rates in placebo and comparator groups were not taken into account when assigning frequency categories to adverse events derived from clinical trial data, since these rates were generally comparable to those in the active treatment group. Rare and very rare events were generally derived from spontaneous data.

Infections and infestations

Very rare: Secondary infection.

Secondary infections, particularly when occlusive dressings are used or when skin folds are involved have been reported with corticosteroid use.

Immune system disorders

Very rare: Hypersensitivity.

If signs of hypersensitivity appear, application should stop immediately.

Endocrine disorders

Very rare: Features of hypercortisolism.

Prolonged use of large amounts of corticosteroids, or treatment of extensive areas, can result in sufficient systemic absorption to produce the features of hypercortisolism. This effect is more likely to occur in infants and children, and if occlusive dressings are used. In infants, the napkin may act as an occlusive dressing (See 4.4 Special Warnings and Special Precautions for Use).

Vascular disorders

Very rare: Dilation of superficial blood vessels.

Prolonged and intensive treatment with potent corticosteroid preparations may cause dilation of the superficial blood vessels.

Skin and subcutaneous tissue disorders

Common: Pruritus.

Uncommon: Local burning.

Very rare: Allergic contact dermatitis, exacerbation of signs and

symptoms of dermatoses, pustular psoriasis. Prolonged and intensive treatment wih potent corticosteroid preparations may cause thinning, striae, hypertrichosis and hypopigmentation.

Treatment of psoriasis with a corticosteroid (or its withdrawal) may provoke the pustular form of the disease.

4.9 Overdose

Acute overdosage is very unlikely to occur, however, in the case of chronic overdosage or misuse, the features of hypercortisolism may appear and in this situation, topical steroids should be discontinued gradually. However, because of the risk of acute adrenal suppression this should be done under medical

supervision.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Fluticasone propionate is a glucocorticoid with high topical anti-inflammatory potency but low HPA-axis suppressive activity after dermal administration. It therefore has a therapeutic index which is greater than most of the commonly available steroids.

It shows high systemic glucocorticoid potency after subcutaneous administration but very weak oral activity, probably due to metabolic inactivation. *In vitro* studies show a strong affinity for, and agonist activity at, human glucocorticoid receptors.

Fluticasone propionate has no unexpected hormonal effects, and no overt, marked effects upon the central and peripheral nervous systems, the gastrointestinal system, or the cardiovascular or respiratory systems.

5.2 Pharmacokinetic properties

Pharmacokinetic data for the rat and dog indicate rapid elimination and extensive metabolic clearance. Bioavailability is very low after topical or oral administration, due to limited absorption through the skin or from the gastrointestinal tract, and because of extensive first-pass metabolism. Distribution studies have shown that only minute traces of orally administered compound reach the systemic circulation, and that any systemically-available radiolabel is rapidly eliminated in the bile and excreted in the faeces.

Fluticasone propionate does not persist in any tissue, and does not bind to melanin. The major route of metabolism is hydrolysis of the S-fluoromethyl carbothioate group, to yield a carboxylic acid (GR36264), which has very weak glucocorticoid or anti-inflammatory activity. In all test animal species, the route of excretion of radioactivity is independent of the route of administration of radiolabelled fluticasone propionate. Excretion is predominantly faecal and is essentially complete within 48 hours.

In man too, metabolic clearance is extensive, and elimination is consequently rapid. Thus drug entering the systemic circulation via the skin, will be rapidly inactivated. Oral bioavailability approaches zero, due to poor absorption and extensive first-pass metabolism. Therefore systemic exposure to any ingestion of the topical formulation will be low.

5.3 Preclinical safety data

Reproductive studies suggest that administration of corticosteroids to pregnant animals can result in abnormalities of foetal development including cleft palate/lip. However, in humans, there is no convincing evidence of congenital abnormalities, such as cleft palate or lip.

Studies of safety pharmacology, repeated dose toxicity, genotoxicity,

carcinogenic potential, fertility and general reproductive performance revealed no special hazard for humans, other than that anticipated for a potent steroid.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Liquid Paraffin

Cetostearyl Alcohol

Isopropyl Myristate

Cetomacrogol 1000

Propylene Glycol

Imidurea

Sodium Phosphate

Citric Acid Monohydrate

Purified Water

6.2 Incompatibilities

None reported.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

15g, 30g, 50g and 100g collapsible internally-laquered, blind-end aluminium tubes, with latex bands and closed with polypropylene caps.

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

No special instructions.

Administrative Data

7. MARKETING AUTHORISATION HOLDER

Glaxo Wellcome UK Ltd T/A Glaxo Laboratories

and / or GlaxoSmithKline UK

Stockley Park West

Uxbridge

Middlesex, UB11 1BT.

8. MARKETING AUTHORISATION NUMBER(S)

PL 10949/0013.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 February 1993.

10. DATE OF REVISION OF THE TEXT

19 February 2007

11. Legal Status

POM.

http://emc.medicines.org.uk/emc/assets/c/html/displaydoc.asp?DocumentID=726

SUPPORTING INFORMATION

Patient Information Leaflet:
Cutivate Cream

Medicine Guide:
Cutivate (new window)

Doc. B

Coreg—Cont.

arate the time of dosing of *Coreg* from that of the ACE inhibitor or to reduce temporarily the dose of the ACE inhibitor. The dose of *Coreg* should not be increased until symptoms of worsening heart failure or vasodilation have been stabilized.

Fluid retention (with or without transient worsening heart failure symptoms) should be treated by an increase in the dose of diuretics.

The dose of *Coreg* should be reduced if patients experience bradycardia (heart rate <55 beats/min).

Episodes of dizziness or fluid retention during initiation of Coreg can generally be managed without discontinuation of treatment and do not preclude subsequent successful titration of, or a favorable response to, carvedilol.

Hypertension

DOSAGE MUST BE INDIVIDUALIZED. The recommended starting dose of *Coreg* is 6.25 mg twice daily. If this dose is tolerated, using standing systolic pressure measured about 1 hour after dosing as a guide, the dose should be maintained for 7 to 14 days, and then increased to 12.5 mg twice daily if needed, based on trough blood pressure, again using standing systolic pressure one hour after dosing as a guide for tolerance. This dose should also be maintained for 7 to 14 days and can then be adjusted upward to 25 mg twice daily if tolerated and needed. The full antihypertensive effect of *Coreg* is seen within 7 to 14 days. Total daily dose should not exceed 50 mg. *Coreg* should be taken with food to slow the rate of absorption and reduce the incidence of orthostatic effects.

Addition of a diuretic to *Coreg*, or *Coreg* to a diuretic can be expected to produce additive effects and exaggerate the orthostatic component of *Coreg* action.

Coreg (carvedilol) should not be given to patients with severe hepatic impairment (see CONTRAINDICATIONS).

HOW SUPPLIED

Tablets: White, oval, film-coated tablets: 3.125 mg–engraved with 39 and SB, in bottles of 100; 6.25 mg–engraved with 4140 and SB, in bottles of 100; 12.5 mg–engraved with 4141 and SB, in bottles of 100; 25 mg–engraved with 4142 and SB, in bottles of 100. The 6.25 mg, 12.5 mg and 25 mg tablets are Tiltab® tablets.

Store below 30°C (86°F). Protect from moisture. Dispense in a tight, light-resistant container.

3.125 mg 100's: NDC 0007-4139-20
6.25 mg 100's: NDC 0007-4140-20
12.5 mg 100's: NDC 0007-4141-20
25 mg 100's: NDC 0007-4142-20

Coreg is a registered trademark.

November 2001/CO:L6

Shown in Product Identification Guide, page 315

CUTIVATE®

℞

[kyoot'ə-vāt]
(fluticasone propionate cream)
Cream, 0.05%

For Dermatologic Use Only—
Not for Ophthalmic Use.

DESCRIPTION

CUTIVATE (fluticasone propionate cream) Cream, 0.05% contains fluticasone propionate [(6α,11β,16α,17 α)-6,9,-difluoro-11-hydroxy-16-methyl-3-oxo-17-(1-oxopropoxy) androsta-1,4-diene-17-carbothioic acid, S-fluoromethyl ester], a synthetic fluorinated corticosteroid, for topical dermatologic use. The topical corticosteroids constitute a class of primarily synthetic steroids used as anti-inflammatory and antipruritic agents.

Chemically, fluticasone propionate is $C_{25}H_{31}F_3O_5S$.

Fluticasone propionate has a molecular weight of 500.6. It is a white to off-white powder and is insoluble in water.

Each gram of CUTIVATE Cream contains fluticasone propionate 0.5 mg in a base of propylene glycol, mineral oil, cetostearyl alcohol, Ceteth-20, isopropyl myristate, dibasic sodium phosphate, citric acid, purified water, and imidurea as preservative.

CLINICAL PHARMACOLOGY

Like other topical corticosteroids, fluticasone propionate has anti-inflammatory, antipruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear. However, corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2.

Fluticasone propionate is lipophilic and has a strong affinity for the glucocorticoid receptor. It has weak affinity for the progesterone receptor, and virtually no affinity for the mineralocorticoid, estrogen, or androgen receptors. The therapeutic potency of glucocorticoids is related to the half-life of the glucocorticoid-receptor complex. The half-life of the fluticasone propionate-glucocorticoid receptor complex is approximately 10 hours.

Table 1: Drug-Related Adv

Adverse Events	Fluticasone Once Daily (n = 210)	I
Skin infection	1 (0.5%)	
Infected eczema	1 (0.5%)	
Viral warts	0	
Herpes simplex	0	
Impetigo	1 (0.5%)	
Atopic dermatitis	1 (0.5%)	
Eczema	1 (0.5%)	
Exacerbation of eczema	4 (1.9%)	
Erythema	0	
Burning	2 (1.0%)	
Stinging	0	
Skin irritation	6 (2.9%)	
Pruritus	2 (1.0%)	
Exacerbation of pruritus	4 (1.9%)	
Folliculitis	1 (0.5%)	
Blisters	0	
Dryness of skin	3 (1.4%)	

Table 2: Adverse Events* From P (n = 51)

Adverse Events	
Burning	
Dusky erythema	
Erythematous rash	
Facial telangiectasia†	
Non-facial telangiectasia	
Urticaria	

*See text for additional detail.
†n = 41.

Studies performed with CUTIVATE Cream indicate that it is in the medium range of potency as compared with other topical corticosteroids.

Pharmacokinetics: ***Absorption:*** The activity of CUTIVATE is due to the parent drug, fluticasone propionate. The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle and the integrity of the epidermal barrier. Occlusive dressing enhances penetration. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption.

In a human study of 12 healthy males receiving 12.5 g of 0.05% fluticasone propionate cream twice daily for 3 weeks, plasma levels were generally below the level of quantification (0.05 ng/mL). In another study of 6 healthy males administered 25 g of 0.05% fluticasone propionate cream under occlusion for 5 days, plasma levels of fluticasone ranged from 0.07 to 0.39 ng/mL.

In an animal study using radiolabeled 0.05% fluticasone propionate cream and ointment preparations, rats received a topical dose of 1 g/kg for a 24-hour period. Total recovery of radioactivity was approximately 80% at the end of 7 days. The majority of the dose (73%) was recovered from the surface of the application site. Less than 1% of the dose was recovered in the skin at the application site. Approximately 5% of the dose was absorbed systemically through the skin. Absorption from the skin continued for the duration of the study (7 days), indicating a long retention time at the application site.

Distribution: Following intravenous administration of 1 mg fluticasone propionate in healthy volunteers, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The apparent volume of distribution averaged 4.2 L/kg (range, 2.3 to 16.7 L/kg). The percentage of fluticasone propionate bound to human plasma proteins averaged 91%. Fluticasone propionate is weakly and reversibly bound to erythrocytes. Fluticasone propionate is not significantly bound to human transcortin.

Metabolism: No metabolites of fluticasone propionate were detected in an in vitro study of radiolabeled fluticasone propionate incubated in a human skin homogenate. The total blood clearance of systemically absorbed fluticasone propionate averages 1093 mL/min (range, 618 to 1702 mL/min) after a 1-mg intravenous dose, with renal clearance accounting for less than 0.02% of the total. Fluticasone propionate is metabolized in the liver by cytochrome P450 3A4-mediated hydrolysis of the 5-fluoromethyl carbothioate grouping. This transformation occurs in 1 metabolic step to produce the inactive 17-β-carboxylic acid metabolite, the only known metabolite detected in man. This metabolite has approximately 2000 times less affinity than the parent drug for the glucocorticoid receptor of human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolites detected in vitro using cultured human hepatoma cells have not been detected in man.

Excretion: Following intravenous dose of 1 mg in healthy volunteers, fluticasone propionate showed polyexponential kinetics and had an average terminal half-life of 7.2 hours (range, 3.2 to 11.2 hours).

INDICATIONS AND USAGE

CUTIVATE Cream is a medium potency corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

Proprietary Name Search Results from "OB_Rx" table for query on "cutivate."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
019958	AB	Yes	FLUTICASONE PROPIONATE	CREAM; TOPICAL	0.05%	CUTIVATE	ALTANA
021152		Yes	FLUTICASONE PROPIONATE	LOTION; TOPICAL	0.05%	CUTIVATE	ALTANA
019957	AB	Yes	FLUTICASONE PROPIONATE	OINTMENT; TOPICAL	0.005%	CUTIVATE	ALTANA

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FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through June, 2007
Patent and Generic Drug Product Data Last Updated: July 19, 2007

Search results from the "OB_Rx" table for query on "019322."

Active Ingredient:	CLOBETASOL PROPIONATE
Dosage Form;Route:	CREAM; TOPICAL
Proprietary Name:	TEMOVATE
Applicant:	ALTANA
Strength:	0.05%
Application Number:	019322
Product Number:	001
Approval Date:	Dec 27, 1985
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	**AB1**
Patent and Exclusivity Info for this product:	View

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
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Doc E

PRESCRIBING INFORMATION

TEMOVATE E®

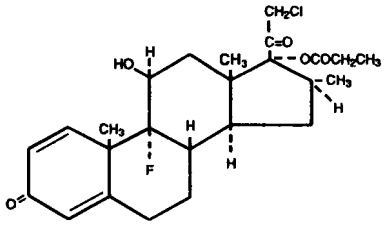
(clobetasol propionate emollient cream) Emollient, 0.05%

FOR TOPICAL DERMATOLOGIC USE ONLY—
NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE

DESCRIPTION

TEMOVATE E (clobetasol propionate emollient cream) Emollient contains the active compound clobetasol propionate, a synthetic corticosteroid, for topical dermatologic use. Clobetasol, an analog of prednisolone, has a high degree of glucocorticoid activity and a slight degree of mineralocorticoid activity.

Chemically, clobetasol propionate is (11β,16β)-21-chloro-9-fluoro-11-hydroxy-16-methyl-17-(1-oxopropoxy)-pregna-1,4-diene-3,20-dione, and it has the following structural formula:



Clobetasol propionate has the empirical formula $C_{25}H_{32}ClFO_5$ and a molecular weight of 467. It is a white to cream-colored crystalline powder insoluble in water.

TEMOVATE E Emollient contains clobetasol propionate 0.5 mg/g in an emollient base of cetostearyl alcohol, isopropyl myristate, propylene glycol, cetomacrogol 1000, dimethicone 360, citric acid, sodium citrate, purified water, and imidurea as a preservative.

CLINICAL PHARMACOLOGY

Like other topical corticosteroids, clobetasol propionate has anti-inflammatory, antipruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear. However, corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2.

Pharmacokinetics: The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle and the integrity of the epidermal barrier. Occlusive dressing with hydrocortisone for up to 24 hours has not been demonstrated to increase penetration; however, occlusion of hydrocortisone for 96 hours markedly enhances penetration. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin may increase percutaneous absorption.

Studies performed with TEMOVATE E Emollient indicate that it is in the super-high range of potency as compared with other topical corticosteroids.

INDICATIONS AND USAGE

TEMOVATE E Emollient is a super-high potency corticosteroid formulation indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. Treatment beyond 2 consecutive weeks is not recommended, and the total dosage should not exceed 50 g/week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis. Use in pediatric patients under 12 years of age is not recommended.

In the treatment of moderate to severe plaque-type psoriasis, TEMOVATE E Emollient applied to 5% to 10% of body surface area can be used up to 4 consecutive weeks. The total dosage should not exceed 50 g/week. When dosing for more than 2 weeks, any additional benefits of extending treatment should be weighed against the risk of HPA suppression. Treatment beyond 4 consecutive weeks is not recommended. Patients should be instructed to use TEMOVATE E Emollient for the minimum amount of time necessary to achieve the desired results (see PRECAUTIONS and INDICATIONS AND USAGE). Use in pediatric patients under 16 years of age has not been studied.

CONTRAINDICATIONS

TEMOVATE E Emollient is contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

PRECAUTIONS

General: Clobetasol propionate is a highly potent topical corticosteroid that has been shown to suppress the HPA axis at doses as low as 2 g/day.

Systemic absorption of topical corticosteroids can produce reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal from treatment. Manifestations of Cushing syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on therapy.

Patients applying a topical steroid to a large surface area or to areas under occlusion should be evaluated periodically for evidence of HPA axis suppression. This may be done by using the ACTH stimulation, A.M. plasma cortisol, and urinary free cortisol tests. Patients receiving super-potent corticosteroids should not be treated for more than 2 weeks at a time, and only small areas should be treated at any one time due to the increased risk of HPA suppression.

In a controlled clinical trial involving patients with moderate to severe plaque-type psoriasis, TEMOVATE E Emollient applied to 5% to 10% of body surface area resulted in additional benefits in the treatment of patients for 4 consecutive weeks. In this trial, there were no clobetasol-treated patients with clinically significant decreases in morning cortisol levels after 4 weeks of treatment; however, morning cortisol levels may not identify patients with adrenal dysfunction. Therefore, the additional benefits of extending treatment beyond 2 weeks should be weighed against the potential for HPA suppression. Therapy should be discontinued when control has been achieved. Treatment beyond 4 consecutive weeks is not recommended.

If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent corticosteroid. Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids. Infrequently, signs

and symptoms of glucocorticosteroid insufficiency may occur that require supplemental systemic corticosteroids. For information on systemic supplementation, see prescribing information for those products.

Pediatric patients may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios (see PRECAUTIONS: Pediatric Use). The use of TEMOVATE E Emollient for 4 consecutive weeks has not been studied in pediatric patients under 16 years of age.

If irritation develops, TEMOVATE E Emollient should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing a *failure to heal* rather than noting a clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

If concomitant skin infections are present or develop, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of TEMOVATE E Emollient should be discontinued until the infection has been adequately controlled.

TEMOVATE E Emollient should not be used in the treatment of rosacea or perioral dermatitis, and should not be used on the face, groin, or axillae.

Information for Patients: Patients using topical corticosteroids should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
2. This medication should not be used for any disorder other than that for which it was prescribed.
3. The treated skin area should not be bandaged, otherwise covered, or wrapped so as to be occlusive unless directed by the physician.
4. Patients should report any signs of local adverse reactions to the physician.
5. Patients should inform their physicians that they are using TEMOVATE if surgery is contemplated.
6. This medication should not be used on the face, underarms, or groin areas.
7. As with other corticosteroids, therapy should be discontinued when control has been achieved. If no improvement is seen within 2 weeks, contact the physician.

Laboratory Tests: The following tests may be helpful in evaluating patients for HPA axis suppression:

ACTH stimulation test
A.M. plasma cortisol test
Urinary free cortisol test

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential of clobetasol propionate.

Studies in the rat following subcutaneous administration at dosage levels up to 50 mcg/kg/day revealed that the females exhibited an increase in the number of resorbed embryos and a decrease in the number of living fetuses at the highest dose.

Clobetasol propionate was nonmutagenic in 3 different test systems: the Ames test, the *Saccharomyces cerevisiae* gene conversion assay, and the *E. coli* B WP2 fluctuation test.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application to laboratory animals.

Clobetasol propionate has not been tested for teratogenicity when applied topically; however, it is absorbed percutaneously, and when administered subcutaneously it was a significant teratogen in both the rabbit and mouse. Clobetasol propionate has greater teratogenic potential than steroids that are less potent.

Teratogenicity studies in mice using the subcutaneous route resulted in fetotoxicity at the highest dose tested (1 mg/kg) and teratogenicity at all dose levels tested down to 0.03 mg/kg. These doses are approximately 1.4 and 0.04 times, respectively, the human topical dose of TEMOVATE E Emollient. Abnormalities seen included cleft palate and skeletal abnormalities.

In rabbits, clobetasol propionate was teratogenic at doses of 3 and 10 mcg/kg. These doses are approximately 0.02 and 0.05 times, respectively, the human topical dose of TEMOVATE E Emollient. Abnormalities seen included cleft palate, cranioschisis, and other skeletal abnormalities.

There are no adequate and well-controlled studies of the teratogenic potential of clobetasol propionate in pregnant women. TEMOVATE E Emollient should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when TEMOVATE E Emollient is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of TEMOVATE E Emollient in pediatric patients have not been established. Use in pediatric patients under 12 years of age is not recommended. For continued use beyond 2 consecutive weeks, the safety of TEMOVATE E Emollient has not been studied. Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of HPA axis suppression and Cushing syndrome when they are treated with topical corticosteroids. They are therefore also at greater risk of adrenal insufficiency during or after withdrawal of treatment. Adverse effects including striae have been reported with inappropriate use of topical corticosteroids in infants and children.

HPA axis suppression, Cushing syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Geriatric Use: A limited number of patients at or above 65 years of age (n = 34) have been treated with TEMOVATE E Emollient in US clinical trials. While the number of patients is too small to permit separate analysis of efficacy and safety, the single adverse reaction reported in this population was similar to those reactions reported by younger patients. Based on available data, no adjustment of dosage of TEMOVATE E Emollient in geriatric patients is warranted.

ADVERSE REACTIONS

In controlled trials with all clobetasol propionate formulations, the following adverse reactions have been reported: burning/stinging, pruritus, irritation, erythema, folliculitis, cracking and fissuring of the skin, numbness of the fingers, tenderness in the elbow, skin atrophy, and telangiectasia. The incidence of local adverse reactions reported in the trials with TEMOVATE E Emollient was <2% of patients treated with the exception of burning/stinging, which occurred in 5% of treated patients.

Cushing syndrome has been reported in infants and adults as a result of prolonged use of other topical clobetasol propionate formulations.

The following additional local adverse reactions are reported infrequently with topical corticosteroids, but may occur more frequently with super-high potency corticosteroids such as TEMOVATE E Emollient. These reactions are listed in an approximately decreasing order of occurrence: dryness, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, striae, and miliaria.

OVERDOSAGE

Topically applied TEMOVATE E Emollient can be absorbed in sufficient amounts to produce systemic effects (see PRECAUTIONS).

DOSAGE AND ADMINISTRATION

Apply a thin layer of TEMOVATE E Emollient to the affected skin areas twice daily and rub in gently and completely (see INDICATIONS AND USAGE).

TEMOVATE E Emollient is a super-high potency topical corticosteroid; therefore, **treatment should be limited to 2 consecutive weeks and amounts greater than 50 g/week should not be used.**

In moderate to severe plaque-type psoriasis, TEMOVATE E Emollient applied to 5% to 10% of body surface area can be used up to 4 weeks. The total dosage should not exceed 50 g/week. When dosing for more than 2 weeks, any additional benefits of extending treatment should be weighed against the risk of HPA suppression. As with other highly active corticosteroids, therapy should be discontinued when control has been achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary. Treatment beyond 4 consecutive weeks is not recommended. Use in pediatric patients under 16 years of age has not been studied.

TEMOVATE E Emollient should not be used with occlusive dressings.

Geriatric Use: In studies where geriatric patients (65 years of age or older, see PRECAUTIONS) have been treated with TEMOVATE E Emollient, safety did not differ from that in younger patients; therefore, no dosage adjustment is recommended.

HOW SUPPLIED

TEMOVATE E Emollient, 0.05% is supplied in:
15-g tubes (NDC 0173-0454-01),
30-g tubes (NDC 0173-0454-02), and
60-g tubes (NDC 0173-0454-03).

Store between 15° and 30°C (59° and 86°F). TEMOVATE E Emollient should not be refrigerated.

GlaxoSmithKline Consumer Healthcare LP
Pittsburgh, PA 15230

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